



**PATENT**  
Attorney Docket No. 207596  
DHHS Reference No. E-200-1998/0-US-02

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of:

Erickson et al.

Art Unit: 1648

Application No. 09/720,276

Examiner: Emily Le

Filed: March 7, 2001

For: **FITNESS ASSAY AND  
ASSOCIATED METHODS**

**DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. HIROAKI MITSUYA**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Hiroaki Mitsuya, hereby declare and state that:

1. I have considerable experience in the area of anti-HIV drug therapy and the problems associated with HIV drug resistance. I received an M.D. in 1975, and a Ph.D. in 1982, from Kumamoto University School of Medicine. I have been conducting medical research at the National Institutes of Health for over twenty years, and specialize in anti-HIV research. I have authored over 250 articles relating to anti-HIV research and have been listed among the top 10 most cited AIDS researchers internationally. I am also on the Editorial Board of several scientific journals, including *Antiviral Research*, *Journal of Enzyme Inhibition*, and *Antiviral Chemistry & Chemotherapy*. I am currently Principal Investigator & Chief at the Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, of the National Cancer Institute. I am also Vice-Director at the University Hospital, National Kumamoto University School of Medicine. A copy of my Curriculum Vitae is attached.

2. I am a named inventor in the above-captioned patent application ("present application").

3. I have studied the efficacy of compounds known as "TMC-114" and "TMC-126" against multi-drug resistant HIV *in vitro*. TMC-114 and TMC-126 are the first and second

compounds, respectively, identified in Table 4, p. 81, of the present application. The antiviral efficacies of TMC-114 and TMC-126 were evaluated against a panel of multiply mutated, multi-drug resistant HIV strains obtained from infected human patients who were not responsive to existing anti-HIV regimens. The results of my research have been published in Koh et al., *Antimicrob. Agents Chemother.*, 47, 3123-3129 (2003); and Yoshimura et al., *J. Virol.*, 76, 1349-1358 (2002), copies of which are attached.

4. TMC-114 and TMC-126 exhibited extremely high and unprecedented broad-spectrum potency against all of the human strains of multi-drug resistant HIV tested in my laboratory. None of the drugs approved in the U.S. for human anti-HIV therapy have exhibited the broad-spectrum potency against multi-drug resistant HIV exhibited by TMC-114 and TMC-126.

5. Structure-based studies, including X-ray crystallographic studies on the enzyme-inhibitor complex, suggest that TMC-114 and TMC-126 interact with HIV protease in regions of the active site that known protease inhibitors do not interact with. The broad-spectrum potency of TMC-114 and TMC-126 against diverse strains of multi-drug resistant HIV is believed to be at least partially attributable to the ability of these compounds to uniquely interact with specific regions in the active site of HIV protease.

6. The research in this field as a whole, including my own research, demonstrates that TMC-114 and TMC-126 should effectively inhibit new strains of multi-drug resistant HIV that emerge in humans undergoing anti-HIV therapy.

7. While it is believed that HIV ultimately can produce strains that are resistant to any existing anti-HIV agent (including TMC-114 and TMC-126), the research in this field as a whole, including my own research, demonstrates that TMC-114 and TMC-126 should significantly delay the emergence of HIV resistance *in vivo*. In this regard, TMC-114 and TMC-126 should significantly prolong the lives of HIV-infected humans who are at risk of dying as a result of multi-drug resistant HIV infection.

8. The research in this field as a whole, including my own research, demonstrates that TMC-114 and TMC-126 should be therapeutically effective for treating existing infections with multi-drug resistant HIV *in vivo*.

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9. The present application provides biological data, e.g., multi-drug resistant HIV antiviral data, including the results of my own research, human protein binding studies, and *in vivo* data. The biological data provided by the present application, in view of the HIV protease inhibitor technology generally known in the art at the time that the present application was filed, demonstrate that the exemplified compounds should be therapeutically effective *in vivo*.

10. Clinical studies have confirmed that TMC-114 is in fact orally efficacious in humans for treating multi-drug -resistant HIV infection. The results of these clinical studies have been disclosed by Arasteh et al., 10<sup>th</sup> CROI, Feb 10-14, 2003, Session 4/Abst# 8, a copy of which is attached.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under/ 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

April 26, 2004  
Date

Hiroaki Mitsuya  
Hiroaki Mitsuya, M.D., Ph.D.

# CURRICULUM VITAE

## Hiroaki Mitsuya, M.D., Ph.D.

Present Address 4601 North Park Avenue, #1010, Chevy Chase, MD 20815  
Phone 301-657-1189  
Birth Date August 9, 1950  
Birth Place Sasebo, Nagasaki, Japan  
Citizenship Japan (US green card holder)

Education

September 1982	Received a Ph.D. degree (Doctor of Medical Science) from Kumamoto University School of Medicine, Honjo 1-1-1, Kumamoto 860, Japan
March 1975	Received an M.D. degree from Kumamoto University School of Medicine
March 1969	Graduated Sasebo North High School, Hachiman-Cho 6-31, Sasebo 857, Japan

Work Experience

July 2001 - Present	Principal Investigator & Chief, Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892
April 2000 - Present	Vice-Director, University Hospital, National Kumamoto University School of Medicine, Kumamoto 860, Japan
April 2000-Present	Director, Department of Infectious Diseases, University Hospital, National Kumamoto University School of Medicine, Kumamoto 860, Japan
April 1998 - Present	Director, Center for Clinical Trials, University Hospital, National Kumamoto University School of Medicine, Kumamoto 860, Japan
April 1997 - Present	Professor of Medicine and Chairman, Department of Internal Medicine II, Kumamoto University School of Medicine, Kumamoto 860, Japan

April 1997 - July 2001

Principal Investigator & Chief, Experimental Retrovirology Section, Medicine Branch, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892

July 1991 - March 1997

Chief, Experimental Retrovirology Section, Medicine Branch, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892

February 1989 - July 1991

Senior Investigator, Clinical Oncology Program, National Cancer Institute, 9000 Rockville Pike, Bethesda, MD 20892.

December 1988 - February 1989

Visiting Scientist, Clinical Oncology Program, National Cancer Institute

February 1984 - December 1988

Cancer Expert, Clinical Oncology Program, National Cancer Institute

October 1983 - February 1984

Visiting Fellow, Clinical Oncology Program, National Cancer Institute

October 1982 - September 1983

Visiting Fellow, Metabolism Branch, National Cancer Institute

February 1980 - September 1982

Instructor, Department of Internal Medicine II, Kumamoto University School of Medicine

April 1977 - January 1980

Research/Clinical Fellow, Department of Internal Medicine II, Kumamoto University School of Medicine

June 1975 - March 1977

Resident, Dept of Internal Medicine II, Kumamoto University School of Medicine

#### Editorial Boards

Editorial Board  
Editorial Board  
Editor

*Antiviral Research*, April 1992 - present  
*Journal of Enzyme Inhibition*, April 1992 - present  
Special Issue on "Inhibitors of HIV-1 Reverse Transcriptase and Protease as Therapeutics of AIDS", *Journal of Enzyme Inhibition*, April issue, 1992

Editorial Board  
Editor

*Antiviral Chemistry & Chemotherapy*, March 1993 - present  
"Anti-HIV nucleosides: Past, Present, and Future", *Molecular Biology Intelligence Unit*, R.G. Landes Company, Austin, 1997.

Editorial Board

Critical Reviews in Oncology/Hematology (1998 - Present)

### Honors and Awards

American Society for Clinical Investigation (Member)

American Association of Immunologists

Fogarty International Visiting Fellow Scholarship, 1982-1983

Invention Award, National Cancer Institute, 1989

Special Act/Service Award, National Cancer Institute, 1990

US Department of Commerce Inventor's Awards -1987, 1989, 1989, 1989, 1990, 1991, 1992, 1995, 1996, 1996, 1996, 1997

NIH Director's Award, National Institutes of Health, 1992

“For important discoveries relating to infection with the human immunodeficiency virus and its therapy”

Outstanding Paper Award, Controlled Release Society, 1993

Anderson, B.D., Baker, D.C., Galinsky, R.E., Hoesterey, B.H., Morgan, M., Murakami, K., and Mitsuya, H.: Approaches toward the optimization of CNS uptake of anti-AIDS agents. *J. Controlled Release*, 19:219-230, 1992.

Among top 10 most cited AIDS researchers internationally, 1988-1992. Appearing in *Science* 260:1262, 1992.

NIH Intramural AIDS Targeted Antiviral Program Fund Award, 1993, 1994

Agents for Change Clinician Scientists Award 2000 (May 2000 in Stockholm; Glaxo-Wellcome) to: Yoshimura, K., Kato, R., Yusa, K., Kavlick, M.F., Maroun, V., Nguyen, A., Mimoto, T., Ueno, T., Shintani, M., Falloon, J., Masur, H., Hayashi, H., Erickson, J., and Mitsuya, H. (1999) JE-2147: a novel dipeptide protease inhibitor (PI) that potently inhibits multi-PI resistant HIV-1. *Proc. Natl. Acad. Sci. USA*, 96: 8675-8680.

### Professional Activities (Selected)

American Federation for Clinical Research

American Association for the Advancement of Science

International Society of Antiviral Research

Special Review Committee for National Institute of Allergy and Infectious Diseases (NIAID) for evaluation of the Multicenter AIDS Cohort Study and Its Data Center, and the San Francisco Men's Health Study, 1991.

Session Organizer for the Gordon Research Conference on Chemotherapy of AIDS, Oxnard, California, March 15-20, 1992

Discussion Leader for the Gordon Research Conference on Chemotherapy of AIDS, Oxnard, California, March 22-26, 1993

International Scientific Advisory Board for the VIth International Antiviral Symposium, Nice, France, June 7-10, 1994

International Program Committee for the Xth International Conference on AIDS, Yokohamam, Japan, August 7-12, 1994

International Scientific Committee for the Conference on Overview and Status of HIV: The Disease, Prevention, and/or Control, Pavia, Italy, October 1-4, 1995

Co-organizer for the Conference on HIV-1 Infection and Cellular Metabolism, S. Patrignano, Corione, Italy, October 5 and 6, 1995

Organizing Committee, Ninth International Conference on Human Retrovirology: HTLV and related viruses, Kagoshima, April 5-9, 1999

Co-Chair, Special Task Force for Guidelines of Antiviral Therapy of HIV-1 Infection, Japan. 1998 - Present.

Governing Council, International AIDS Society. 1999 - present.

Scientific Committee, HIV DART 2002, Frontiers in Drug Development from Antiretroviral Therapies, Naples, Florida, December 15-19, 2002.

Scientific Programme Committee, The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, July 13-17, 2003

International Program Committee for the XVth International Conference on AIDS, Bangkok, Thailand, July 11-16, 2004.

#### Other Responsibilities

Chairman, The Board of Directors, Washington, D.C. Japanese Language School (Non-profit Organization). January 1993 to December 1993

### Selected Major Invited Lectureships

Plenary Speaker (Invited)	UCLA Symposium on "Human Retroviruses, Cancer, and AIDS: Approaches to Prevention and Therapy", Keystone, Colorado, April 1-6, 1987
Plenary Speaker (Invited)	UCLA Symposium on "Mechanisms of Action and Therapeutic Applications of Biologicals in Cancer and Immune Deficiency Disorders", Keystone, Colorado, April 23-30, 1988
Plenary Speaker (Invited)	FASEB Summer Conference on "Molecular Biology and Infectious Diseases", Copper Mountain, Colorado, July 17-22, 1988
Plenary Speaker (Invited)	Symposium on Human Retroviruses and AIDS, Taipei, Republic of China, November 11-13, 1988
Plenary Speaker (Invited)	UCLA Symposium on "Human Retroviruses", Tamarron, Colorado, February 4-11, 1989
Speaker (Invited)	International Workshop on "Pathogenesis and Prevention of Hepatocellular Carcinoma", Oahu, Hawaii, February 13-15, 1989
Speaker (Invited)	XIth International Symposium for Comparative Research on Leukemia and Related Diseases, Denver and Vail, Colorado, October 7-12, 1989
Plenary Speaker (Invited)	Royal Society of Medicine Meeting on Applications of Biotechnology in Therapeutics and Preventive Medicine, Southampton, England, December 4-6, 1989
Speaker (Invited)	First International Workshop on Viral Quantitation in HIV Infection, Paris, France, June 13-14, 1991
Speaker and Session Organizer (Invited)	Gordon Research Conference on "Chemotherapy of AIDS", Oxnard, CA, March 15-20, 1992
Plenary Speaker (Invited)	Vth World Conference on Clinical Pharmacology and Therapeutics, Yokohama, Japan, July 26-31, 1992
Plenary Speaker (Invited)	First Asian Pacific Congress of Allergology and Immunology, Bangkok, Thailand, November 22-26, 1992



Speaker and Discussion Leader (Invited)	Gordon Research Conference on "Chemotherapy of
Plenary Speaker (Invited)	Keystone Symposium on "Frontiers in HIV Pathogenesis", Albuquerque, New Mexico, March 29-April 4, 1993
Plenary Speaker (Invited)	18th Int'l Congress of Chemotherapy, Stockholm, Sweden, June 27-July 2, 1993
Speaker (Invited)	Second International Workshop on Viral Quantitation in HIV Infection, Paris, France, June 3-4, 1993.
Speaker (Invited)	1st International Meeting on Myotoxicity and Neurotoxicity of Antiretroviral Nucleotide Analogues, L'Aquila and Rome, Italy, March 19-25, 1994
Speaker and Scientific Advisory Board	VIth International Antiviral (Invited) Symposium, Nice, France, June 7-10, 1994
Round-Table Session Organizer and	Xth International Conference on International Program Committee (Invited) AIDS, Yokohama, Japan, August 7-12, 1994
Speaker, Chairman, International Scientific Committee (Invited)	The Conference on Overview and Status of HIV: The Disease, Prevention, and Control, Pavia, Italy, October 1-4, 1995
Co-organizer, Speaker, Chairman (Invited)	The First International Conference on HIV-1 Infection and Cellular Metabolism, S. Patrignano, Corione, Italy, October 5 and 6, 1995
Speaker (Invited)	New Research Trends in Immunological Diseases, Second Green Cross International Symposium, Osaka, Japan, October 20-21, 1995.
Speaker (Invited)	Symposium on Molecular Insights into the Targets of HIV-1 Therapy. Stanford, California, May 10, 1996.
Speaker (Invited)	The Japanese Society for Investigative Dermatology 21st Annual Meeting, Tokyo, Japan, July 26-27, 1996.

Speaker (Invited)	Course 6, "STD and AIDS" in the 19th World Congress of Dermatology, Sydney, Australia, June 15-20, 1997.
Speaker (Invited)	Japan-France AIDS Cooperative Study Conference, Tokyo, Japan, December 4-5, 1998
Speaker (Invited)	International Symposium on HIV, Leukemia and Opportunistic Cancers, organized by Harvard AIDS Institute, May 23-28, 1999, Marrakech, Morocco
Speaker (Invited)	US-Japan AIDS Cooperative Study Conference, Toyama, Japan, March 17-19, 1999.
Speaker and Steering Committee	US-Japan AIDS Cooperative Study Conference, Santa Fe, March 17-19, 2000.
Speaker (Invited) and Advisory Board	8th International Antiviral Symposium, Kagoshima, Japan, November 19-21, 2000.
Co-organizer	US-Japan AIDS Cooperative Study Conference, Kumamoto, March 21-24, 2001.
Speaker and Steering Committee	US-Japan AIDS Cooperative Study Conference, Seattle, WA, March 17-19, 2002.
Moderator	26th International Congress of Internal Medicine, Kyoto, May 26-29, 2002
Speaker (Invited) and Scientific Committee	HIV DART 2002: Frontiers in Drug Development of Antiretroviral Therapies, Naples, Florida, December 15-19, 2002
Speaker and Steering Committee	US-Japan AIDS Cooperative Study Conference, Okinawa, Japan, March 5-7, 2003.
Speaker and Moderator	10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 11-15, 2003.
Moderator and Scientific Committee	The 2nd IAS Conference on HIV Pathogenesis and Treatment, Paris, France, July 13-17, 2003
Speaker and Steering Committee	US-Japan AIDS Cooperative Study Conference, Nashville, Tennessee, March 8-10, 2004.

## MAJOR REVIEWS:

1. MITSUYA, H. and Broder, S. Strategies for anti-retroviral therapy of patients with AIDS. *Nature*, 325:773-778, 1987.
2. MITSUYA, H., Yarchoan, R., and Broder, S.: Molecular targets for antiviral therapy against AIDS. *Science*, 249:1533-1544, 1990.
3. MITSUYA, H., Yarchoan, R., Kageyama, S., and Broder, S. Targeted therapy of human immunodeficiency virus-related disease. *FASEB J.* 5:2369-2381, 1991.
4. MITSUYA, H. Overview: Development of inhibitors of reverse transcriptase and protease as therapeutics against HIV infection. *J. Enzyme Inhibition.* 6:1-8, 1992.
5. MITSUYA, H. and Yarchoan, R. Development of antiretroviral therapy for AIDS and related disorders. In "*Textbook of AIDS Medicine*" (ed. Broder, S., Merigan, T., and Bolgnesi, D.), Williams & Wilkins, Baltimore, pp. 721-742, 1994
6. Anderson, B.D. and MITSUYA, H. Reverse transcriptase as a target for AIDS therapy. In "*Design of Enzyme Inhibitors as Drugs, Volume 2*" (Ed. M. Sandler and H.J. Smith) Oxford University Press, Oxford, pp.290-332, 1994
7. MITSUYA, H. "*Anti-HIV nucleosides: Past, Present, and Future*", (Ed. H. Mitsuya), R.G. Landes Company, Austin, 1997.
8. MITSUYA, H. and Erickson, J. Discovery and development of antiretroviral therapeutics for HIV infection. In: *Textbook of AIDS medicine*, edited by Merigan, Bartlett, and Bolgnesi, Williams & Wilkins, Baltimore, pp. 751-780, 1999.
9. Kavlick, M.F. and MITSUYA, H. Emergence of drug resistant HIV-1 variants and their impact on antiretroviral therapy of HIV-1 infection. In "*The Art of Antiretroviral Therapy*" (Ed. Erik De Clercq) American Society for Microbiology, Washington, D.C. pp. 279-312, 2001

**Bibliography**  
**Hiroaki Mitsuya, M.D., Ph.D.**

1. Kishimoto, S., Tomino, S., Inomata, K., Kotegawa, S., Saito, T., Kuroki, M., Mitsuya, H., and Hisamitsu, S.: Age-related changes in the subsets and functions of human T lymphocytes. *J. Immunol.* 121:1773-1770, 1978.
2. Mitsuya, H., Tomino, S., Hisamitsu, S., and Kishimoto, S.: Evidence for the failure of IgA specific T helper activity in a patient with immuno-deficiency with hyper-IgM. *J. Clin. Lab. Immunol.* 2:337-342, 1979.
3. Kishimoto, S., Tomino, S., Mitsuya, H., and Fujiwara, H.: Age-related changes in human suppressor T lymphocytes. *J. Immunol.* 123:1586-1593, 1979.
4. Kishimoto, S., Tomino, S., Mitsuya, H., Fujiwara, H., and Tsuda, H. Age-related decline in the *in-vitro* and *in-vivo* synthesis of antitetanus toxoid antibody in humans. *J. Immunol.* 125:2347-2353, 1980.
5. Kishimoto, S., and Mitsuya, H.: Immunosenescence and defense mechanisms. *Asian Medical J.* 23:558-563, 1980.
6. Mitsuya, H., Matsukura, M., Tomino, S., Fujiware, and Kishimoto, S.: T cell suppression of immunoglobulin synthesis in ataxia telangiectasia: Restruction of suppressor activity to B cells from unrelated donors. *Clin. Immunol. Immunopathol.* 19:383-393, 1981.
7. Mitsuya, H., Osaki, K., Tomino, S., Katsuki, T., and Kishimotor, S.: Patholophysiological analysis of peripheral blood lymphocytes from patients with primary immunodeficiency. I. Ig synthesis by peripheral blood lymphocytes stimulated with either pokeweed mitogen or Epstein-Barr virus *in-vitro*. *J. Immunol.* 127:311-315, 1981.
8. Kishimoto, S., Tomino, S., Mitsuya, H., and Nishimura, H.: Age-related decrease in frequencies of B-cell precursors and specific helper T cells involved in the IgG anti-tetanus toxoid antibody production in humans. *Clin. Immunol. Immunopathol.* 24:1-11, 1982.
9. Mitsuya, H.: Immunologic analysis of peripheral blood lymphocytes from patients with primary immunodeficiency. *J. Japanese Med.* (in English) 21:65-68, 1982.
10. Tomino, S., Fujiwara, H., Kagimoto, T., Mitsuya, H., Nishimura, H., and Kishimoto, S.: Decreased suppressor T cell activity in patients with hepatic cirrhosis (HC). *Clin. Exp. Immunol.* 48:625-632, 1982.
11. Mitsuya, H., Sato, M., Hirano, T., Fujimoto, K., Kawano, F., and Kishimoto, S.: Evidence for a malignant proliferation of IgE-class specific helper T cells in a patient

with Sezary syndrome exhibiting massive hyperimmunoglobulinemia E. *Clin. Immunol. Immunopathol.* 26:171-183, 1983.

12. Matsuzaki, H., Yamaguchi, K., Hara, H., Mitsuya, H., Kawano, F., Araki, K., Tanaka, R., and Kishimoto, S.: Simultaneous occurrence of acute leukemia and multiple myeloma without previous chemotherapy. *Scand. J. Haematol.* 30:278-286, 1983.
13. Mitsuya, H., Matis, L., Megson, M., Bunn, P.A., Murray, C., Mann, D.L., Gallo, R.C., and Broder, S.: Generations of HLA-restricted cytotoxic T-cell line reactive against cultured tumor cells from a patient infected with human T-cell leukemia/lymphoma virus (HTLV). *J. Exp. Med.* 158:994-999, 1983.
14. Miyayama, H., Takemiya, M., Takahashi, K., Sasazaki, Y., Sato, M., and Mitsuya, H.: Massive IgE-hyperimmunoglobulinemia and storage histiocytosis in Sezary syndrome. *Cancer*, 53:1869-1877, 1984.
15. Mitsuya, H. and Broder, S.: Cytotoxic T cells specific for human T-cell leukemia/lymphoma virus (HTLV). In: *Human T cell Leukemia Virus*, (ed. Gallo RC, Essex M, Gross L) Cold Spring Harbor Laboratory, New York pp. 229-235, 1984.
16. Tsuchiya, H., Higuchi, S., Kuwahara, T., Matsuda, I., Mitsuya, H., and Yamaguchi, K.: Immunologic studies of peripheral blood in a child with hypogammaglobulinemia. *Cancer*, 53:1492-1497, 1984.
17. Mitsuya, H., Matis, L.A., Megson, M., Cohen, O.J., Mann, D.L., Gallo, R.C., and Broder, S.: Immune T-cells reactive against human T-cell leukemia/lymphoma virus (HTLV). *Lancet*, i:649-652, 1984.
18. Mitsuya, H., Guo, H.G., Megson, M., Trainer, C., Reitz, M.S. Jr., and Broder, S.: Transformation and cytopathogenic effect in an immune human T-cell clone infected by HTLV-I. *Science*, 223:1293-1296, 1984.
19. Mitsuya, H., Guo, H.G., Cossman, J., Megson, M., Reitz, M.S. Jr., Broder, S.: Functional properties of antigen-specific T-cells infected by human T-cell leukemia-lymphoma virus (HTLV-I). *Science*, 225:1484-1486, 1984.
20. Mitsuya, H., Popovic, M., Yarchoan, R., Matsushita, S., Gallo, R.C., Broder, S.: Suramin protection of T cells *in vitro* against infectivity and cytopathic effect of HTLV-III. *Science*, 226:172-174, 1984.
21. Mitsuya, H., and Broder, S.: Clinical features of human T-cell leukemia/lymphoma virus (HTLV) associated T-cell neoplasia. In *Genetic and Phenotypic Markers of Tumors*. (Ed. P.K. Vogt) Plenum Press, New York, pp. 357-372, 1985.
22. Mitsuya, H. and Broder, S.: Human T-cell leukemia/lymphoma viruses (HTLV): A unique family of pathogenic retroviruses. *Curr. Top. Microbiol. Immunol.* 115:33-51, 1985.

23. Mitsuya, H., Matsushita, S., Harper, M.E., and Broder, S.: Pharmacologic inhibition of infectivity of HTLV-III *in vitro*. *Cancer Research*, 45:4583s-4587s, 1985.
24. Yarchoan, R., Mitsuya, H., Matsushita, S., and Broder, S.: Implication of the discovery of HTLV-III for the treatment of AIDS. *Cancer Research*, 45:4685s-4688s, 1985.
25. Tomita, S., Ambrus, J.L., Volkman, D.J., Longo, D.L., Mitsuya, H., Reitz, M.S. Jr., and Fauci, A.S.: Human T-cell leukemia/lymphoma virus (HTLV)-I transformation and subsequent cloning of normal human B cells: Direct responsiveness of cloned cells to recombinant interleukin 2 by differentiation in the absence of enhanced proliferation. *J. Exp. Med.* 162:393-398, 1985.
26. Broder, S., Yarchoan, R., Collins, J.M., Lane, H.C., Marcham, P.D., Klecker, R.W., Redfield, R.R., Mitsuya, H., Hotch, D.F., Gelmann, E., Groopman, J.E., Resnick, L., Gallo, R., Myers, C.E., and Fauci, C.E.: Effects of suramin on HTLV-III/LAV infection presenting as Kaposi's sarcoma or AIDS-related complex: Clinical pharmacology and suppression of virus replication *in vivo*. *Lancet*, ii, 627-630, 1985.
27. Mitsuya, H., Weinhold, K.J., Furman, P.A., St. Clair, M.H., Lehrman, S.N., Gallo, R.C., Bolognesi, D., Barry, D.W., and Broder, S.: 3'-azido-3'-deoxy-thymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus *in vitro*. *Proc. Natl. Acad. Sci. USA*. 82:7096-7100, 1985.
28. Mitsuya, H., Matsushita, S., Yarchoan, R., and Broder, S.: Protection of T-cells against infectivity and cytopathic effect of HTLV-III *in vitro*. In: *Retroviruses in Human Lymphoma/Leukemia*. ed. M. Miwa et al. Japan Sci. Soc. Press, Tokyo/VNU Science Press, Utrecht, pp. 277-288, 1985.
29. Jarrett, R.F., Mitsuya, H., Mann, D.L., Cossman, J., Broder, S., Gallo, R.C., and Reitz, M.S.: Configuration and expression of the gene encoding the b-chain of the T-cell receptor in HTLV-I infected cells. *J. Exp. Med.* 163:383-399, 1986.
30. Mitsuya, H., and Broder, S.: Inhibition of the *in vitro* infectivity and cytopathic effect of HTLV-III/LAV by 2', 3'-dideoxynucleosides. *Proc. Natl. Acad. Sci. USA*. 83:1911-1915, 1986.
31. Matsushita, S., Robert-Guroff, M., Trepel, J., Cossman, J., Mitsuya, H., and Broder, S.: Human monoclonal antibody against an envelope glycoprotein of human T-cell leukemia virus type-I. *Proc. Natl. Acad. Sci. USA*. 83:2672-2676, 1986.
32. Kotani, H., Mitsuya, H., Jarrett, R.F., James, S.P., and Strober, W.: An autoreactive T cell clone which can be activated to provide both helper and suppressor function. *J. Immunol.* 136:1951-1959, 1986.

33. Yarchoan, R., Klecker, R.W., Weinhold, K.J., Durack, D.T., Gelmann, E.D., Lehrman, S.N., Blum, R.M., Barry, D.W., Shearer, G.M., Fischl, M.A., Mitsuya, H., Gallo, R.C., Collins, J.M., Bolognesi, D.P., Myers, C.E., and Broder, S.: Treatment of AIDS or AIDS-related complex with 3'-azido-3'-deoxythymidine, an inhibitor of HTLV-III/LAV replication. *Lancet*, i:575-580, 1986.
34. Balzarini, J., Mitsuya, H., Cleron, E.D., and Broder, S.: Comparative inhibitory effects of suramin and other selected compounds on the infectivity and replication of human T-cell lymphotropic virus (HTLV-III)/lymphadenopathy-associated virus (LAV). *Int. J. Cancer*, 37:451-457, 1986.
35. Balzarini, J., Mitsuya, H., Clercq, E.D., and Broder, S.: Aurintricarboxylic acid and evans blue represent two different classes of anionic compounds which selectively inhibit the cytopathic effect of human T-lymphotropic virus/lymphadenopathy-associated virus. *Biochem. Biophys. Res. Commun.* 136:64-71, 1986.
36. Yarchoan, R., Guo, H.G., Reitz, M. Jr., Maluish, A., Mitsuya, H., and Broder, S.: Alterations in cytotoxic and helper T cell function following infection of T cell clones with HTLV-I. *J. Clin. Invest.*, 77:1466-1473, 1986.
37. Cooney, D.A., Dalal, M., Mitsuya, H., McMahon, J.B., Nadkarni, M., Balzarini, J., Broder, S., and Johns, D.G.: Initial studies on the cellular pharmacology of 2', 3'-dideoxycytidine, an inhibitor of HTLV-III infectivity. *Biochem. Pharmacol.* 35:2065-2068, 1986.
38. Fisher, A.G., Ratner, L., Mitsuya, H., Marselle, L.M., Harper, M.E., Broder, S., Gallo, R.C., and Wong-Staal, F.: Infectious mutants of HTLV-III with changes in the 3' region and markedly reduced cytopathic effects. *Science*, 233:655-659, 1986.
39. Kantoff, P.W., Kohn, D.B., Mitsuya, H., Armentano, D., Sieberg, M., Zwiebel, J.A., Eglitis, M.A., McLachlin, J.R., Wiginton, D.A., Hutton, J.J., Horowitz, S.D., Gilboa, E., Blaese, R.M., and Anderson, W.F.: Correction of adenosine deaminase deficiency in cultured human T and B cells by retroviral-mediated gene transfer. *Proc. Natl. Acad. Sci. USA*, 83:6563-6567, 1986.
40. Mitsuya, H., Jarrett, R.F., Cossman, J., Cohen, O.J., Whang-Peng, J., Guo, H.G., Reitz, M.S. Jr., and Broder, S.: Infection of human T-lymphotropic virus-I (HTLV-I)-specific immune T-cell clones by HTLV-I. *J. Clin. Invest.* 78:1302-1310, 1986.
41. Furman, P.A., Fyfe, J.A., St. Clair, M.H., Weinhold, K., Rideout, J.L., Freeman, G.A., Lehrman, S.N., Bolognesi, D.P., Broder, S., Mitsuya, H. and Barry, D.: Mode of inhibition of the human T-cell lymphotropic virus III by 3'-azido-3'-deoxythymidine. *Proc. Natl. Acad. Sci. USA* 83:8333-8337, 1986.
42. Mitsuya, H., Yarchoan, R., and Broder, S.: 2', 3'-dideoxynucleoside analogues: Development of anti-viral therapy for HTLV-III/LAV associated diseases. *Tropical Med.* 28s:119-126, 1986.

43. Mitsuya, H., Matsukura M., and Broder, S.: Rapid *in vitro* systems for assessing activity of agents against HTLV-III/LAV. In *AIDS: Modern Concepts and Therapeutic Challenge* (ed. Broder, S.) Marcel-Dekker, New York. pp. 303-333, 1987.
44. Mitsuya, H. and Broder, S. Strategies for anti-retroviral therapy of patients with AIDS. *Nature*, 325:773-778, 1987.
45. Mitsuya, H., Jarrett, R.F., Matsukura M., Di Marzo Veronese, F., Devico, A.L., Sarngadharan, M.G., Johns, D.G., Reitz, M.S., and Broder, S.: Long-term inhibition of HTLV-III/LAV DNA synthesis and RNA expression in T-cells protected by 2', 3'-dideoxynucleosides. *Proc. Natl. Acad. Sci. USA*. 84:2033-2037, 1987.
46. Dahlberg, J.E., Mitsuya, H., Broder, S., and Aaronson, S.A.: 2', 3'-dideoxynucleosides: Broad spectrum anti-retroviral activity. *Proc. Natl. Acad. Sci. USA*. 84:2469-2473, 1987.
47. Matsushita, S., Mitsuya, H., Reitz, M.S., and Broder, S.: Pharmacological inhibition of *in vitro* infectivity of human T-lymphotropic virus type I (HTLV-I). *J. Clin. Invest.* 80:394-400, 1987.
48. Narumiya, S., Hirata, M., Nanba, T., Nikaldo, T., Taniguchi, Y., Tagaya, Y., Okada, M., Mitsuya, H., and Yodoi, J.: Activation of interleukin-2 receptor gene by forskolin and cyclic AMP analogues. *Biochem. Biophys. Research Commu.* 143:753-760, 1987.
49. Antonen, J., Mitsuya, H., and Krohn, K.: The use of a HTLV-I infected human T-cell line ATH8 in interleukin-2 assay. *J. Immunol. Method.* 99:271-275, 1987.
50. Kim, C.H., Marquez, V.E., Broder, S., Mitsuya, H., and Driscoll, J.S.: Potential anti-AIDS drugs. 2', 3'-dideoxycytidine analogs. *J. Med. Chem.* 30:862-877, 1987.
51. Cooney, D.A., Ahluwalia, G., Mitsuya, H., Fridland, A., Johnson, M., Hao, Z., Dalal, M., Balzarini, J., Broder, S., and Johns, D.: Initial studies on the cellular pharmacology of 2', 3'-dideoxyadenosine, and inhibitor on HTLV-III infectivity. *Biochem. Pharmacol.* 36:1765-1768, 1987.
52. Ratner, L., Fisher, A., Jagodzinski, L.L., Mitsuya, H., Liou, R.S., Gallo, R.C., and Wong-Staal, F.: Complete nucleotide sequences of functional clones of the virus associated with the acquired immunodeficiency syndrome, HTLV-III/LAV. *AIDS Res. Hum. Retroviruses*, 3:57-69, 1987.
53. Ahluwalia, G., Cooney, D.A., Mitsuya, H., Fridland, A., Flora, K.P., Hao, Z., Dalal, M., Broder, S., and Johns, D.G.: Initial studies on the cellular pharmacology of 2', 3'-dideoxyinosine, an inhibitor of HIV infectivity. *Biochem. Pharm.* 36:3797-3800, 1987.
54. Matsukura, M., Shinozuka, K., Zon, G., Mitsuya, H., Broder, S., and Cohen, J.S.: Phosphorothioate analogs of oligodeoxynucleotides as novel inhibitors of replication and



cytopathic effects of HTLV-III (Human Immunodeficiency Virus). *Proc. Natl. Acad. Sci. USA.* 84:7706-7710, 1987.

55. Marquez, V.E., Tseng, C.K.H., Kelley, J.A., Roth, J.S., Mitsuya, H., Broder, S., and Driscoll, J.S.: 2', 3'-dideoxy-2'-fluoro-ara-A: An acid stable purine nucleoside analog active against human immunodeficiency virus. *Biochem. Pharm.* 36:2719-2722, 1987.
56. Yarchoan, R., Perno, C.F., Thomas, R.V., Klecker, R.W., Allain, J.P., Wills, R.J., McAtee, N., Fischl, M.A., Dubinsky, R., McNeely, C., Mitsuya H., Pluda, J.M., Lawley, T.J., Leuther, M., Safai, B., Collins, J.M., Meyers, C.E., and Broder, S.: Administration of 2', 3'-dideoxycytidine to patients with severe human immunodeficiency virus infection as a single agent in an alternating regimen with 3'-azido-2', 3'-dideoxythymidine (AZT). *Lancet*, i: 76-81, 1988.
57. Mitsuya, H., Dahlberg, J.E., Spigelman, Z., Matsushita, S., Jarrett, R.F., Matsukura, M., Currens, M.J., Aaronson, S.A., Reitz, M.S., McCaffrey, R.S., and Broder, S.: 2', 3'-dideoxynucleosides: Broad spectrum antiretroviral activity and mechanism of action. In: *Human Retrovirus, Cancer, and AIDS: Approaches to Prevention and Therapy*, (Ed. D. Bolognesi), Alan R. Liss, Inc., New York, 1988, pp. 407-421.
58. Spigelman, Z., Duff, R., Beardsley, G.P., Broder, S., Landau, N.R., Mitsuya, H., Ullman, B., and McCaffrey, R.: 2', 3'-dideoxyadenosine selectively kills primitive lymphoid cells. *Blood*, 71:1601-1608, 1988.
59. Vidal, C., Matsushita, S., Colamonici, O.R., Trepel, J.B., Mitsuya, H., and Neckers, L.: HTLV-I infection deregulates surface expression of the transferrin receptor. *J. Immunol.* 141:984-988, 1988.
60. Mitsuya, H. and Broder, S.: Progress in the therapy of human immunodeficiency virus (HIV) infections. In: *Retrovirus Biology and Human Disease*. (ed. Gallo, R.C. and Wong-Staal, F.) Marcel-Dekker, New York, 1991, pp. 331-358.
61. Webb, R.W., Mitsuya, H., and Broder, S.: 1-(2', 3'-anhydro-beta-D-lyxofuranosyl)cytosine derivatives as potential inhibitors of the human immunodeficiency virus. *J. Med. Chem.* 31:1475-1479, 1988.
62. Surbone, A., Yarchoan, R., McAtee, N., Blum, M.R., Maha, M., Allain, J.P., Thomas, R.V., Mitsuya, H., Lehrman, S.N., Leuther, M., Pluda, J.M., Jacobsen, F.K., Kessler, H.A., Myers, C.E., and Broder, S. Treatment of Acquired immunodeficiency syndrome (AIDS) and AIDS-related complex (ARC) with a regimen of 3'-azido-2', 3'-dideoxythymidine (AZT) and acyclovir: A pilot study. *Ann. Int. Med.* 108:534-540, 1988.
63. Mitsuya, H., and Broder, S.: Inhibition of infectivity and replication of HIV-2 and SIV in helper T-cells by 2', 3'-dideoxynucleosides *in vitro*. *AIDS Res. Hum. Retrov.* 4:107-113, 1988.

64. Kotani, H., Mitsuya, H., Benson, E., James, S.P., and Strober, W.: Activation and function of an autoreactive T cell clone with dual immunoregulatory activity. *J. Immunol.* 140:4167-4172, 1988.
65. Mitsuya, H., Looney, D.J., Kuno, S., Ueno, R., Wong-Staal, F., and Broder, S.: Dextran sulfate suppression of viruses in the HIV family: Inhibition of virion binding to CD4<sup>+</sup> cells. *Science*, 240:646-649, 1988.
66. Yarchoan, R., Mitsuya, H., and Broder, S.: The therapeutic strategies in the treatment of AIDS. In: *Annual Reports in Medicinal Chemistry*, vol. 23, 1988, pp. 253-263.
67. Mitsuya, H. and Broder, S.: Targeted therapy against human immunodeficiency virus (HIV). In: *ISI Atlas of Science, Immunology*, 1988, pp. 85-94.
68. Mitsuya, H., Yarchoan, R., Hayashi, S., and Broder, S.: Antiviral therapy in human immunodeficiency virus (HIV) infection. *J. Am. Acad. Dermatol.* 22:1282-1294, 1990.
69. Greengrass, C.W., Hoople, D.W.T., Street, S.D.A., Hamilton, F., Marriott, M.S., Borner, J., Dalglish, A.G., Mitsuya, H., and Broder, S.: 1-(3-Cyano-2', 3'-dideoxy-bp-D-erythro-pentofuranosyl) thymine, "Cyanothymidine": Synthesis and antiviral evaluation against human immunodeficiency virus. *J. Med. Chem.* 32:618-622, 1989.
70. Hayashi, S., Phadtare, S., Zemlicka, J., Matsukura, M., Mitsuya, H., and Broder, S.: Adenallene and cytallene, two novel cyclic nucleoside derivatives active against human immunodeficiency virus (HIV) in T-cells and monocytes/macrophages *in vitro*: Further characterization of anti-viral and cytotoxic activity. In: *Mechanisms of Action and Therapeutic Application of Biologicals in Cancer and Immune Deficiency Syndrome*, (ed. J. Groopman, C. Evans, and D. Golde), Alan R. Liss, Inc., New York, 1989, pp. 371-383.
71. Richman, D.D., Mitsuya, H., Broder, S., and Hostetler, K.Y.: Fusidic acid, HIV, and host cell toxicity. *Lancet*, i:1051-1052, 1988.
72. Hayashi, S., Phadtare, S., Zemlicka, J., Matsukura, M., Mitsuya, H., and Broder, S.: Adenallene and cytallene: Acyclic nucleosides that inhibit replication and cytopathic effect of human immunodeficiency virus (HIV) *in vitro*. *Proc. Natl. Acad. Sci. USA.* 85:6127-6131, 1988
73. Mitsuya, H., Looney, D.J., Kuno, S., Ueno, R., Wong-Staal, F., and Broder, S.: Inhibition of virion binding to CD4<sup>+</sup> cells: Suppression of human immunodeficiency viruses by anionic polysaccharides. In: *Mechanisms of Action and Therapeutic Application of Biologicals in Cancer and Immune Deficiency Syndrome* (ed. J. Groopman, C. Evans, and D. Golde), Alan R. Liss, Inc., New York, 1989, pp. 331-341.
74. Mitsuya, H. and Broder, S.: Second generation antiviral therapy against human immunodeficiency virus (HIV). In: *Mechanisms of Action and Therapeutic Application*

of *Biologicals in Cancer and Immune Deficiency Syndrome* (ed. J. Groopman, C. Evans, and D. Golde), Alan R. Liss, Inc., New York, 1989, pp. 343-359.

75. Matsukura, M., Zon, G., Shinozuka, K., Stein, C.A., Mitsuya, H., Wong-Staal, F., Cohen, J.S., and Broder, S.: Synthesis of phosphorothioate analogues of oligodeoxynucleotides and its antiviral activity against human immunodeficiency virus (HIV). *Gene*, 72:343-347, 1988.
76. Yarchoan, R., Mitsuya, H., and Broder, S.: AIDS therapy. *Scientific American*, 256:110-119, 1988.
77. Matsukura, M., Zon, G., Sinozuka, K., Robert-Guroff, M., Shimada, T., Stein, C.A., Mitsuya, H., Wong-Staal, F., Cohen, J.S., and Broder, S.: Regulation of viral expression of HIV (Human Immunodeficiency Virus) *in vitro* by an antisense phosphorothioate oligodeoxynucleotide against *rev* (*art/trs*) in chronically infected cells. *Proc. Natl. Acad. Sci. USA*. 86:4244-4248, 1989.
78. Kohn, D.B., Mitsuya, H., Ballow, M., Selegue, J.E., Barankiewicz, J., Cohen, A., Gelfand, E., Anderson, W.F., and Blaese, R.M.: Establishment and characterization of adenosine deaminase (ADA)-deficient human T-cell lines. *J. Immunol.* 142:3971-3977, 1989.
79. Norbeck, D.W., Spanton, S., Broder, S., and Mitsuya, H. ( $\pm$ )-dioxolane-T: A new 2', 3'-dideoxynucleosides prototype with *in vitro* activity against HIV. *Tetrahedron Lett.*, 30:6263-6266, 1989.
80. Yarchoan, R., Mitsuya, H., Myers, C.E., and Broder, S.: Antiretroviral therapy of HIV infection: Clinical pharmacology of 3'-azido-2', 3'-dideoxythymidine (AZT) and related dideoxynucleosides. *New Eng. J. Med.* 321:726-738, 1989.
81. Capon, D.J., Chamow, S.M., Mordenti, J., Martsters, S.A., Gregory, T., Mitsuya, H., Byrn, R.A., Lucas, C., Wurm, F.M., Groopman, J.E., Broder, S., and Smith, D.H. Designing CD4 immunoadhesions for AIDS therapy. *Nature* 337:525-531, 1989.
82. Perno, C.F., Yarchoan, R., Cooney, D.A., Hartman, N.R., Webb, D.S.A., Hao, Z., Mitsuya, H., Johns, D.G., and Broder, S.: Replication of HIV in monocytes: Granulocyte-macrophage colony stimulating factor (GM-CSF) potentiates viral production yet enhances the antiviral effect mediated by AZT and other dideoxynucleoside congeners of thymidine. *J. Exp. Med.* 169:933-951, 1989.
83. Yarchoan, R., Mitsuya, H., and Broder, S.: Strategies for the combination therapy of HIV infection. *J. Acquired Immune Defic. Syndr.* 3:99s-103s, 1990.
84. Suzuki, H., Okubo, A., Yamazaki, S., Suzuki, K., Mitsuya, H., and Toda, S.: Inhibition of the infectivity and cytopathic effect of human immunodeficiency virus by water-soluble lignin in an extract of the culture medium of *Lentinus edodes Mycelia* (LEM). *Biochem. Biol. Res. Comm.* 160:367-373, 1989.

85. Masood, R., Ahluwalia, G.S., Cooney, D.A., Hao, Z., Marques, V.E., Mitsuya, H., Broder, S., and Johns, D.G.: 2'-Fluoro-2',3'-dideoxyarabinosyladenine: a metabolically stable analogue of the antiretroviral agent 2',3'-dideoxyadenosine. *Mol. Pharmacol.* 37:590-62, 1990.
86. Yarchoan, R., Mitsuya, H., and Broder, S.: Clinical and basic advances in the antiretroviral therapy of human immunodeficiency virus infection. *Am. J. Med.* 87:191-200, 1989.
87. Yarchoan, R., Mitsuya, H., Thomas, R.V., Pluda, J.M., Hartman, N.R., Perno, C.F., Marczyk, K.S., Allain, J.P., Johns, D.G., and Broder, S.: *In vivo* antiviral activity against HIV and favorable toxicity profile of the purine analogue 2', 3'-dideoxyinosine (ddI). *Science*, 245:412-415, 1989.
88. Mitsuya, H., Hayashi, S., Yarchoan, R., Aoki, S., Currens, M.J., Matsukura, M., Broder, S.: Strategy of targeted antiretroviral therapy against human immunodeficiency virus (HIV). In: *Human Retroviruses*. ed. J.E. Groopman, I., Chen, M. Essex, and R. Weiss. Alan R. Liss, Inc. New York, 1990, pp. 239-259.
89. Hayashi, S., Fine, R., Chou, T.C., Broder, S., and Mitsuya, H. *In vitro* inhibition of the infectivity and replication of human immunodeficiency virus type-1 by combination of anti-retroviral 2', 3'-dideoxynucleosides and viral binding inhibitors. *Antimicrob. Agents Chemother.* 34:82-88, 1990.
90. Hayashi, S., Norbeck, D.W., Rosenbrook, W., Matsukura, M., Plattner, J.J., Broder, S., and Mitsuya, H.: Cyclobut-A and G: Carbocyclic oxetanocin analogues that inhibit the replication of human immunodeficiency virus in T-cells and monocytes/macrophages *in vitro*. *Antimicrob. Agents Chemother.* 34:287-294, 1990.
91. Mitsuya, H., and Broder, S.: Antiretroviral chemotherapy against human immunodeficiency virus (HIV) infection: Perspective for therapy of hepatitis B virus infection. *Cancer Detection and Prevention*, 14:299-308, 1989.
92. Yarchoan, R., Pluda, J.M., Mitsuya, H., and Broder, S.: Treatment of acquired immunodeficiency syndrome. In: *Cancer Chemotherapy and Biological Response Modifiers* (ed. Pinedo, H.M., Longo, D.L., and Chabner, B.A.) Elsevier, Netherlands, 1990, pp. 379-415.
93. Looney, D.J., Hayashi, S., Nicklas, M., Redfield, R.R., Broder, S., Wong-Staal, F., and Mitsuya, H.: Differences in the interaction of HIV-1 and HIV-2 with soluble CD4. *J. Acq. Immun. Def. Synd.* 3:649-657, 1990.
94. Kassianides, C., Hoofnagle, J.H., Miller, R.H., Doo, E., Ford, H., Broder, S., and Mitsuya, H.: Inhibition of duck hepatitis virus replication by 2', 3'-dideoxycytidine: A potent inhibitor of reverse transcriptase. *Gastroenterology* 97:1275-1280, 1989.

95. Marquez, V.E., Tseng, C.K.H., Mitsuya, H., Aoki, S., Kelley, J.A., Ford, H. Jr., Roth, J.S., Broder, S., and Driscoll, J.S.: Acid-stable 2'-fluoro-dideoxy-purine nucleosides as active agents against HIV. *J. Med. Chem.* 33:978-985, 1990.
96. Tam, S. Holman, M., Klein, R.S., Mitsuya, H., and Broder, S.: Synthesis and evaluation of 2', 3'-dideoxy-9-deazaadenosine and some related derivatives. *Nucleosides & Nucleotides*, 8:1109-1110, 1989.
97. Hartman, N.R., Johns, D.G., and Mitsuya, H.: Pharmacokinetic analysis of dextran sulfate in rats as pertains to its clinical usefulness for therapy of HIV infection. *AIDS Res. Hum Retrov.* 6:805-812, 1990.
98. Tyler, R.P., Phillips, L.R., Biddle, J.A., Thakker, D.R., Eagan, W., Aoki, S., and Mitsuya, H.: Synthesis of acyloxyalkyl acylphosphonates as potential prodrugs of the antiviral, trisodium phosphonoformate (Foscarnet sodium). *Tetrahedron Lett.* 31:7141-7144.
99. Frank, K.B., Connell, E.V., Holman, M.J., Huryn, D.M., Sluboski, B.C., Tam, S.Y., Todaro, L.J., Weigele, M., Richman, D.D., Mitsuya, H., Broder, S., and Sim, I.S.: Anti-HIV activity of Ro24-5098, an isomer of 2', 3'-dideoxyadenosine: Its anabolism and mechanism of action. *Ann. New York Acad. Sci.* 616:408-414, 1990.
100. Lee, S.J., Fisher, A.G., Looney, D.J., Kao, V.F., Mitsuya, H., Ratner, L., and Wong-Staal, F.: Role of the carboxyl-terminal portion of the HIV-1 transmembrane protein in viral transmission and cytopathogenicity. *AIDS Res. Hum. Retrov.* 5:441-449, 1989.
101. McGowan, J.J., Tomaszewski, J.E., Cradock, C.K., Grieshaber, S., Broder, S., and Mitsuya, H.: An overview of preclinical development of an antiretroviral agent, 2', 3'-dideoxyinosine (ddI). *Rev. Infec. Diseases*, 12:S513-521, 1990.
102. Yarchoan, R., Mitsuya, H., Pluda, J.M., Marczyk, K.S., Thomas, R.V., Hartman, N.R., Brouwers, P., Perno, C.F., Allain, J.P., Johns, D.G., and Broder, S.: The National Cancer Institute phase I study of ddI in adults with AIDS or AIDS-related complex: Analysis of activity and toxicity profiles. *Rev. Infec. Diseases*, 12:S522-533, 1990.
103. Wright, J., Gunter, K.C., Mitsuya, H., Kelly, K., and Siebenlist, U.: Expression of a zinc finger gene in HTLV-1 and HTLV-II transformed cells. *Science*, 248:588-591, 1990.
104. Tseng, C.K.H., Marquez, V.E., Milne, G.W.A., Mitsuya, H., Shirasaka, T., Wysocki, R.J., and Driscoll, J.S.: A ring-enlarged oxetanocin A analogue as an inhibitor of HIV infectivity. *J. Med. Chem.* 34:343-349, 1991.
105. Mitsuya, H., and Broder, S.: Toward rational design of antiretroviral therapy for AIDS. In: *The Human Retroviruses* (ed. R.C. Gallo and G. Jay) Academic Press, Inc., 1991, pp. 335-378.
106. Yarchoan, R., Pluda, J.M., Thomas, R.V., Mitsuya, H., Browers, P., Marczyk, K., Hartman, N., Hones, D.G., and Broder, S.: Long-term activity/toxicity profile of 2', 3'-

- dideoxyinosine (ddI) in the treatment of AIDS or AIDS-related complex. *Lancet*, ii, 526-529, 1990.
107. Mitsuya, H., Shirasaka, T., and Broder, S.: Principle of development of antiviral therapy against HIV. In: *Design of Anti-AIDS Drugs*. (ed. E. De Clercq), Elsevier, New York, 1990, pp. 25-61.
  108. Maruyama, T., Sato, Y., Hori, T., Shiota, H., Nitta, K., Shirasaka, T., Mitsuya, H., and Honjo, M.: Synthesis and antiviral activities of carbocyclic oxetanocin analogues. *Chem. Pharm. Bull.* 38:2719-2725, 1990.
  109. Yarchoan, R., Mitsuya, H., and Broder, S.: Immunologic issues in antiretroviral therapy. *Immunology Today* 11:327-333, 1990.
  110. Hartman, N.R., Ahluwalia, G.S., Cooney, D.A., Mitsuya, H., Kageyama, S., Fridland, A., Broder, S., and Johns, D.G. : Inhibition of IMP dehydrogenase stimulate the phosphorylation of the anti-HIV nucleosides 2',3'-dideoxyadenosine and 2',3'-dideoxyinosine. *Mol. Pharmacol.* 40:118-124, 1991.
  111. Shirasaka, T., Watanabe, K., Yoshioka, H., Kojima, E., Aoki, S., Murakami, K., and Mitsuya, H.: Lipophilic 6-halo-2', 3'-dideoxypurine nucleosides: potential antiretroviral agents targeting HIV-associated neurologic disorders. In: *Advances in Molecular Biology and Targeted Treatment for AIDS* (ed. A. Kumar), Plenum Publishing Co., Washington, D.C. 1991, pp. 323-333.
  112. Ahluwalia, G., Cooney, D.A., Bondoc, L.L. Jr., Currens, J.M., Ford, H., Johns, D.G., Mitsuya, H., and Fridland, A.: Inhibitors of IMP dehydrogenase stimulate the phosphorylation of the nativiral nucleoside 2', 3'-dideoxyguanosine. *Biochem. Biophys. Res. Comm.* 171:1297-1303, 1990.
  113. Shimada, T., Fujii, H., Maier, B., Hayashi, S., Mitsuya, H., Broder, S. and Nienhuis, A.W. Trial of antisense RNA inhibition of HIV replication and gene expression. *Antiviral Chem. Chemother.* 2:133-142, 1991.
  114. Kelley, K., Davis, P., Mitsuya, H., Irving, S., Wright, J., Grassman, R., Fleckenstein, B., Wano, Y., Greene, W., and Siebenlist, U. A high proportion of early response genes are constitutively activated in T cells by HTLV-I. *Oncogene*, 7:1463-1470, 1992.
  115. Mitsuya, H., Yarchoan, R., and Broder, S.: Molecular targets for antiviral therapy against AIDS. *Science*, 249:1533-1544, 1990.
  116. Aoki, S., Yarchoan, R., Thomas, R.V., Pluda, J.M., Marczyk, K., Broder, S., and Mitsuya, H.: Quantitative analysis of HIV-1 DNA in peripheral blood mononuclear cells from patients with AIDS or ARC: Decrease of viral DNA content following treatment with dideoxyinosine (ddI). *AIDS Res. Hum. Retrov.* 6:1331-1339, 1990.

117. Norbeck, D., Kern, E., Hayashi, S., Rosenbrook, W., Sham, H., Herrin, T., Plattner, J.P., Brickson, J., Clement, J.J., Swanson, R., Shipkowitz, N., Hardy, D., Marsh, K., Arnett, G., Shannon, W., Broder, S., and Mitsuya, H.: Cyclobut-A and cyclobut-G: Broad spectrum antiviral agents with potential utility for the therapy of AIDS. *J. Med. Chem.* 33:1281-1285, 1990.
118. Shirasaka, T., Murakami, K., Ford, H., Kelley, J., Yoshioka, H., Kojima, E., Aoki, S., Driscoll, J.S., Broder, S., and Mitsuya, H.: Halogenated congeners of 2', 3'-dideoxypurine nucleosides active against HIV *in vitro*: A new class of lipophilic prodrugs. *Proc. Natl. Acad. Sci. USA.* 87:9426-9430, 1990.
119. Yarchoan, R., Pluda, J.M., Perno, C.F., Mitsuya, H., Thomas, R.V., Wyvill, and Broder, S. (1990) Initial clinical experience with dideoxynucleosides as single agents and in combination therapy. *Ann. New York Acad. Sci.* 616:328-343.
120. Hartman, N.R., Johns, D.G., and Mitsuya, H. (1990) Pharmacokinetic study of dextran sulfate in rats. *Ann. New York Acad. Sci.* 616:523-525.
121. Huryn, D.M., Sluboski, B.C., Tam, S.Y., Todaro, L.J., Weigele, M., Sim, I.S., Frank, K.B., Richman, D.D., Mitsuya, H., and Broder, S. (1990) synthesis and anti-HIV activity of a novel series of isomeric dideoxynucleosides. *Ann. New York Acad. Sci.* 616:530-534.
122. Williams, G.J., Colby, C.B., Schinazi, R.F., Sommadossi, J.-P., Chu, C.K., Johns, D.G., and Mitsuya, H. (1990) The cellular metabolism of AzdU. Correlation with *in vitro* anti-HIV and cytotoxic activities. *Ann. New York Acad. Sci.* 616:620-623.
123. Yarchoan, R., Pluda, J.M., Federico-Perno, C., Mitsuya, H., and Broder, S. Current strategies and future targets for the anti-retroviral therapy of HIV infection. *Blood*, 78:859-884, 1991
124. Aoki-Sei, S., O'Brien, M.C., Ford, H., Fujii, H., Gilbert, D.A., Cooney, D.A., Broder, S. and Mitsuya, H. *In vitro* inhibition of hepatitis B virus replication by 2',3'-dideoxynucleosids: inhibitors of reverse transcriptase. *J. Infect. Dis.* 164:843-851, 1991.
125. Barchi, J.J., Marquez, V.E., Driscoll, J.S., Ford, H. Jr., Mitsuya, H., Shirasaka, T., Aoki, S., and Kelley, J.A.: Potential CNS anti-AIDS drugs. Lipophilic, adenosine deaminase-activated prodrugs. *J. Med. Chem.* 34:1647-1655, 1991.
126. Aoki-Sei, S. and Mitsuya, H. Quantitative analysis of HIV-1 in clinical specimens from patients with HIV-1 infection by polymerase chain reaction (PCR) In: *Implications for Prognosis and Drug Monitoring* (ed. J.-M. Andrieu). John Libbey Eurotext, Paris, 1991, pp.161-170.
127. Murakami, K., Shirasaka, T., Yoshioka, H., Kojima, E., Aoki, S., Ford, H. Jr., Driscoll, J.S., Kelley, J.A., and Mitsuya, H.: *Escherichia coli*-mediated biosynthesis and *in vitro* anti-HIV activity of lipophilic 6-halo-2',3'-dideoxypurine nucleosides. *J. Med. Chem.* 34:1606-1612, 1991.

128. Mitsuya, H.: Preclinical study of anti-HIV drugs. pp. 604-607. In: Broder S., moderator, Antiretroviral therapy in AIDS. *Ann. Intern. Med.* 113:604-618, 1990.
129. Pluda, J.M., Mitsuya, H., and Yarchoan, R.: Hematologic effects of AIDS therapies. In: *Hematology/Oncology Clinics of North America: Hematologic and Oncologic Aspects of HIV Diseases*. (Ed. Mitsuyasu, R.T. and Golde, D.W.) Vol.5, 1991, pp. 229-248.
130. Matsukura, M., Mitsuya, H., and Broder, S.: A new concept in AIDS treatment: an antisense approach and its current status toward clinical application In: *Prospects for Antisense Nucleic Acid Therapy of Cancer and AIDS* (ed. JAH Murphy) Wiley-Liss, New York, 1991. pp. 159-178.
131. Anderson, B.D., Baker, D.C., Galinsky, R.E., Hoesterey, B.H., Morgan, M., Murakami, K., and Mitsuya, H.: Approaches toward the optimization of CNS uptake of anti-AIDS agents. *J. Controlled Release*, 19:219-230, 1992.
132. Mitsuya, H., Yarchoan, R., Kageyama, S., and Broder, S. (1991) Targeted therapy of human immunodeficiency virus-related disease. *FASEB J.* 5:2369-2381.
133. Yarchoan, R., Mitsuya, H., and Broder, S. (1992) Antiretroviral approaches to the therapy of AIDS and related disorders. In "Forum on HIV, 1992" pp. 233-250, 1992.
134. Shimada, T., Fujii, H., Mitsuya, H., and Nienhuis, A.W.: Targeted and highly efficient gene transfer into CD4<sup>+</sup> cells by a recombinant HIV retroviral vector. *J. Clin. Invest.* 88:1043-1047, 1991.
135. Bondoc, L.L. Jr, Robbins, B.L., Ahluwalia, G.S., Mitsuya, H., Friedland, A., and Johns, D. Modulation of metabolism and anti-HIV-1 activity of purine 2',3'-dideoxynucleosides by IMP dehydrogenase inhibitors. *Adv. Exp. Med. Biol.* 309A:49-53, 1991.
136. Fried, M.W., Korenman, J.C., Di Bisceglie, A.M., Park, Y., Waggoner, J.C., Mitsuya, H., Hartman, N.R., Yarchoan, R., Broder, S., and Hoofnagel, J.H. A short-term pilot study of 2',3'-dideoxyinosine for the treatment of chronic hepatitis B. *Hepatology* 16: 861-864, 1992.
137. Iyer, R.P., Phillips, L.R., Biddle, J.A., Thakker, D.R., Egan, W., Aoki, S., and Mitsuya, H. (1989) Synthesis of acyloxyalkyl acylphosphonates as potential products of the antiviral, trisodium phosphonoformate (Foscarnet sodium). *Tetrahedron Lett.* 30: 7141-7144.
138. Kageyama, S., Mimoto, T., Murakawa, Y., Nomizu, M., Ford, H., Shirasaka, T., Gulnik, S., Erickson, J., Takada, K., Hayashi, H., Broder, S., Kiso, Y., and Mitsuya, H. (1993) In vitro anti-HIV activity of transition-state mimetic HIV protease inhibitors containing allophenylnorstatine. *Antimicrob. Agents Chemother.* 37:810-817.



139. Yarchoan, R., Mitsuya, H., and Broder, S. (1992) The immunology of HIV infection: Implications for therapy. *AIDS Res. Hum. Retrov.* 8: 1023-1031.
140. Kojima, E., Shirasaka, T., Machida, M., Yoshioka, H., Murakami, K., and Mitsuya, H. (1991) Synthesis and structure-activity relationships of 2',3'-dideoxypurine nucleosides as potential antiretroviral agents. *Nucleic Acids Symp. Ser.* 25:91-2.
141. Mitsuya, H. (1992) Overview: Development of inhibitors of reverse transcriptase and protease as therapeutics against HIV infection. *J. Enzyme Inhibition.* 6:1-8.
142. Megati, S., Goren, Z., Silverton, J.V., Orlina, J., Nishimura, H., Shirasaka, T., Mitsuya, H., and Zemlicka, J. (1992) R-(-)- and S-(+)-Adenallene: Synthesis, absolute configuration, enantioselectivity of antiretroviral effect and enzymic deamination. *J. Med. Chem.* 35:4098-4104.
143. Kageyama, S., Weinstein, J.N., Shirasaka, T., Kempf, D.J., Norbeck, D.W., Plattner, J.J., Erickson, J., and Mitsuya, H. (1992) In vitro inhibition of HIV-1 replication by C<sub>2</sub> symmetry-based HIV protease inhibitors as single agents or in combinations. *Antimicrob. Anticancer Chemother.* 36: 926-933, 1992.
144. Huryn, D.M., Sluboski, B.C., Tam, S.Y., Weigele, M., Sim, I., Anderson, B., Mitsuya, H., and Broder, S. (1992) Synthesis and anti-HIV activity of iso-nucleosides. *J. Med. Chem.* 35:2347-2354.
145. Shirasaka, T., O'Brien, M., C., and Mitsuya, H. (1993) In vitro evaluation of experimental agents for anti-HIV activity. In "Current Protocols in Immunology" (eds. Colligan, J.E., Kruisbeek, A. M., Margulies, D.H., Shevach, E.M., Strober, W.) vol 1. Suppl 8. Unit 12.9. pp. 12.9.1-12.9.21.
146. Morgan, M.E., Chi, S.-C., Murakami, K., Mitsuya, H., and Anderson, B.D. (1992) Central Nervous system targeting of 2',3'-dideoxyinosine via adenosine deaminase-activated 6-halo-dideoxypurine prodrugs. *Antimicrob. Agents Chemother.* 36:2156-2165.
147. Siddiqui, M.A., Driscoll, J.S., Kelley, J.A., Roth, J.S., Mitsuya, H., Shirasaka, T., Barchi, J.J., and Marquez, V.E. (1992) Chemistry and anti-HIV properties of 2'-fluoro-2',3'-dideoxyarabinofuranosyl pyrimidines. *J. Med. Chem.* 35:2195-2201, 1992.
148. Aoki-Sei, S., Yarchoan, R., Kageyama, S., Hoekzema, D.T., Pluda, J.M., Wyvill, K.M., Broder, S., and Mitsuya, H. (1992) Plasma HIV-1 viremia in HIV-1 infected individuals assessed by polymerase chain reaction. *AIDS Res. Hum. Retroviruses*, 8:1269-1276, 1992.
149. Shirasaka, T., Yarchoan, R., O'Brien, M.C., Husson, R.N., Anderson, B.D., Kojima, E., Broder, S., and Mitsuya, H. (1993) Changes in drug sensitivity of human immunodeficiency virus type 1 during therapy with azidothymidine, dideoxycytidine, and dideoxyinosine: An in vitro comparative study. *Proc. National Acad. Sci. USA* 90: 562-566.

150. Johns, D.G., Ahluwalia, G.S., Cooney, D.A., Mitsuya, H., and Driscoll, J.S. (1993) Enhanced stimulation by ribavirin of the 5'-phosphorylation and anti-human immunodeficiency virus activity of 2'- @[--- Unable To Translate ---] agasaki A, Seto M, Yoshida M, Kuribayashi N, Kimura T, Harada N, Mitsuya H, and Matsuzaki H. (1998) Amplification and overexpression of the PRAD1/Cyclin D1 gene in a multiple myeloma cell line. *Int J Hematol.* 68:459-461.
  213. Humphrey, R.W., Ohagen, Å., Davis, D.A., Fukazawa, T., Hayashi, H., Hoglund, S., Mitsuya, H., and Yarchoan, R. (1998) Removal of human immunodeficiency virus type 1 (HIV-1) protease inhibitors from preparations of immature HIV-1 virions does not result in an increase in infectivity or the appearance of mature morphology. *Antimicrob. Agents Chemother.* 41:1017-1023.
  214. Gao, W.-Y., Zhou, B.-S., Johns, D.G., Mitsuya, H., and Yen, Y. (1998) Role of the M2 subunit of ribonucleotide reductase in potentiation by hydroxyurea of the anti-HIV-1 agent 2',3'-dideoxyinosine. *Mol. Pharmacol.* 56:105-112.
  215. Kavlick, M.F., Wyvell, K., Yarchoan, R., and Mitsuya, H. (1998) Emergence of multi-dideoxynucleoside resistant HIV-1 variants, viral sequence variation, and disease progression in patients receiving antiretroviral chemotherapy. *J. Infect. Dis.* 98:1506-1513.
  216. Rezende, L.F., Curr, K., Ueno, T., Mitsuya, H., and Prasad, V.R. (1998) The impact of nucleoside analog resistance mutations in human immunodeficiency virus type 1 reverse transcriptase on mutation rates and error specificity. *J. Virol.* 72: 2890-2895.
  217. Maeda, Y., Venzon, D.J., and Mitsuya, H. (1998) Altered drug sensitivity and fitness of HIV-1 with pol gene mutations conferring multi-dideoxynucleoside resistance. *J. Infect. Dis.* 177:1207-1213.
  218. Winter, H., Maeda, Y., Uchida, H., Mitsuya, H., and Zemlicka, J. (1997) Phosphodiester amidates of unsaturated nucleoside analogues: Synthesis and anti-HIV activity. *J. Med. Chem.* 40: 2191-2195.
  219. Marquez, V.E., Ezzitouni, A., Russ, P., Siddiqui, M.A., Feldman, R.J., Mitsuya, H., George, C., and Barchi, J.J., Jr. (1998) HIV-1 reverse transcriptase discriminates between two conformationally locked carbocyclic AZT-triphosphate analogues. *J. Am. Chem. Soc.* 120: 2780-2789.
  220. Roth, J.S., Ford, H., Tanaka, M., Mitsuya, H., and Kelley, J.A. (1998) Determination of 2'- @[--- Unable To Translate Text Box ---]
- 2,3-bis-hydroxymethyl)methylenecyclopropane analogues of purine nucleosides. *Nucleosides Nucleotides Nucleic Acids.* 22:265-274.
279. Depboylu, C; T. A. Reinhart; W. J. Schwaeble; M. K.-H. Schäfer; H. Maeda; H. Mitsuya; R. Damadzic; D. M. Rausch; L. E. Eiden; and E. Weihe. (2003) Brain C1q biosynthesis

is increased in SIV infection in the Rhesus macaque, and is directly related to brain virus burden. *Neuroscience* (under revision)

280. Tamamura, H., Koh, Y., Ueda, S., Sasaki, Y., Yamasaki, T., Aoki, M., Maeda, K., Warai, Y., Arikuni, H., Otaka, A., Mitsuya, H., and Fujii, N. (2003) Reduction of peptide character of HIV protease inhibitors that exhibit nanomolar potency against multi-drug resistant HIV-1 strains. *J. Med. Chem.* 46:1764-1768.
281. Choi, Y., George, C., Comin, M.J., Barchi, J.J., Jr., Kim, H.S., Jacobson, K.A., Balzarini, J., Mitsuya, H., Boyer, P.L., Hughes, S.H., and Marquez, V. E. (2003). A conformationally locked analogue of the anti-HIV agent stavudine. An important correlation between pseudorotation and maximum amplitude. *J Med Chem* 46:3292-3299.
282. Takeyama, K., Ogura, M., Morishima, Y., Kasai, M., Kiyama, Y., Ohnishi, K., Mitsuya, H., Kawano, F., Masaki, Y., Sasaki, T., Chou, t., Yokozawa, T., Tobinai, K., and members for the Lenograstim/Lymphoma Study Group. (2003) A dose-finding study of glycosylated G-CSF (Lenograstim) combined with CHOP therapy for stem cell mobilization in patients with non-Hodgkin's lymphoma. *Jpn J. Clin. Oncol.* 33:78-85.
283. Yoshimura, K., Ido, E., Akiyama, H., Kimura, T., Aoki, M., Suzuki, H., Mitsuya, H., Hayami, M., and Matsushita, S. (2003) The impact of HAART by oral route on the CD8 subset and turnover in the chronically SHIV89.6P-infected monkeys. *J. Virol. Methods.* 112:121-128
284. Koh, Y., Nakata, H., Maeda, K., Ogata, H., Bilcer, G., Devasamudram, T., Kincaid, J.F., Boross, P., Wang, Y.-F., Tie, Y., Volarath, P., Gaddis, L., Louis, J.M., Harrison, R.W., Weber, I.T., Ghosh, A.K., and Mitsuya, H. (2003) Novel *bis*-tetrahydrofuran-yl-urethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC114) potent against multi-PI-resistant human immunodeficiency virus in vitro. *Antimicrob. Agents Chemother.* 47:3123-3129.
285. Wang, R., Harada, S., Mitsuya, H., and Zemlicka, J. (2003) Inhibition of Human Immunodeficiency Virus Reverse Transcriptase by Synadenol Triphosphate and Its E-Isomer. *J. Med. Chem.* 46:4799-4802
286. Kohgo, S., Yamada, K., Kitano, K., Sakata, S., Hayakawa, H., Nameki, D., Kodama, E., Matsuoka, M., Mitsuya, H., and Ohnishi, H. (2003). Synthesis of 4'-C-ethynyl and 4'-C-cyano purine nucleosides from natural nucleosides and their anti-HIV activity. *Nucleosides Nucleotides Nucleic Acids* 22:887-889.
287. Matsuno, N., Osato, M., Yamashita, N., Yanagida, M., Nanri, T., Fukushima, T., Motoji, T., Kusumoto, S., Towatari, M., Suzuki, R., Naoe, T., Nishii, K., Shigesada, K., Ohno, R., Mitsuya, H., Ito, Y. and Asou, N. (2003). Dual mutations in the AML1 and FLT3 genes are associated with leukemogenesis in acute myeloblastic leukemia of the M0 subtype. *Leukemia* 17:2492-2499.
288. Maeda, K., Nakata, H., , Y., Miyakawa, t., Ogata, H., Takaoka, Y., Shibayama, s., Sgawa, K., Fukushima, d., Moravek, J., Koyanagi, Y., and Mitsuya, H. (2003) A novel

pirodiketopiperazine-based CCR5 inhibitor which preserves CC-chemokine/CCR5 interactions and exerts potent activity against R5 HIV-1 *in vitro* and *in vivo*. *J. Virol.* (In press)

## **First Clinical Results on Antiretroviral Activity, Pharmacokinetics, and Safety of TMC114, an HIV-1 Protease Inhibitor, in Multiple PI-experienced Patients**

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**Background:** TMC114 is a Protease Inhibitor (PI) with potent in vitro antiviral activity against wild-type and PI-resistant HIV-1. The study objective was to evaluate the activity, safety, and pharmacokinetics of TMC114 with low dose ritonavir (TMC114/r) in multiple PI-experienced patients (pts) currently failing a PI-containing regimen at study entry.

**Methods:** Open, randomized Phase IIa study in 50 multiple PI-experienced pts. TMC114/r was substituted for the failing PI(s); all other ARVs were not changed. Pts received TMC114/r at doses of 300/100 mg bid (A: n = 13), 600/100 mg bid (B: n = 12), 900/100 mg qd (C: n = 13) or continued the failing regimen (D: n = 12). Pts received TMC114/r for 14 days after which it was discontinued and changes in ART were permitted.

**Results:** Median baseline plasma HIV-1 RNA for the study group was 4.3 log<sub>10</sub> and median baseline CD4 cell count was 297/μL. Median number of previously used PIs was: A:3, B:3, C:4, D:3. Median number of PIs within the range of drug susceptibility (Antivirogram) was A:1, B:1, C:0, and D:1. The median number of primary PI mutations was A:7, B:6, C:7, and D:8. In the ITT analysis, the median change in plasma HIV-1 RNA (log<sub>10</sub>) from baseline to day 14 in arms A, B, C and D was -1.24, -1.50, -1.13 and +0.02 (p < 0.001). The range of HIV-1 RNA reduction in the treatment arms was -0.47 to -2.5 log<sub>10</sub> (median -1.35). In arms A, B, C, and D, 69%, 92%, 69%, and 17% had at least a 1.0 log<sub>10</sub> reduction in HIV-1

RNA, respectively, and in the TMC114/r groups, 97% had at least a 0.50 log<sub>10</sub> reduction from baseline.

Median TMC114 C<sub>min</sub> and AUC<sub>24h</sub> at day 14 in Arms A, B, and C were 1.2 µg/ml and 53.3 µg.h/ml, 1.4 µg/ml and 60.4 µg.h/ml, and 1.6 µg/ml and 67.9 µg.h/ml, respectively.

Treatment with TMC114/r was generally well tolerated. The most commonly reported AEs were GI events. One (1) pt in arm C discontinued treatment due to GI discomfort and 1 pt in arm B had an SAE (hepatitis). Overall, in the TMC114/r arms, 2, 2, and 1 pts had a grade 3/4 ALT, AST or GGT elevations, respectively. One (1) pt in the control group had a grade 3 AST.

**Conclusions:** TMC114/r exhibited potent antiretroviral activity and favorable pharmacokinetics when given for 14 days to multiple PI-experienced pts currently failing a PI-containing regimen. For the TMC114/r arms, maximum and median changes in HIV-1 RNA (log<sub>10</sub>) were -2.49 and -1.35 copies/ml, respectively. TMC114/r was generally well tolerated.